REMARKS

The office action dated October 12, 2005 has been carefully

5   considered. This Amendment, taken with the following remarks, is believed

sufficient to place the present application in condition for allowance.

Reconsideration and an early allowance are respectfully requested.

Claim 1 has been amended to incorporate the recitations of original

claims 3 and 20, which have accordingly been cancelled. As it is believed that

10   this amendment does not involve the addition of new matter, entry and

consideration are respectfully requested.

Claims 1-93 are pending, claims 18,19, 23-28, 30-37 and 43-93 are

withdrawn from prosecution, and claims 1, 2, 4-17, 21-22, 29 and 38-42 are

currently subject to examination.

15   **35 U.S.C. § 112, second paragraph; indefinite**

Claims 1-17, 20-22, 29 and 38-42 are rejected under 35 U.S.C. § 112,

second paragraph, as being indefinite. Specifically, the Examiner asserts that

the use of Genbank accession numbers in claims renders them vague and

indefinite because Genbank accession numbers are not stable over time. The

20   Examiner points to one species noted by Applicants in Table 1, in particular,

of an example of an Accession No. which was replaced in Genbank in 1999,

such that the sequence disclosed in the Genbank reference prior to filing is not

the same as the sequence which is currently in Genbank under this disclosed

accession number. Hence, there are currently more than one sequences which

25   may be accurately referred by the same accession number, and it is not clear to

which the Applicant refers. This rejection is traversed and reconsideration is

respectfully requested.

While Applicants readily admit this attribute of Genbank classification, Applicants note that while the sequence comprising a gene may change over time, therefore altering the sequence associated with a particular accession number over time, the gross "identity" of that gene does not change. This makes it more appropriate, within the pattern concept of the present invention, to focus on the gene being identified, rather than the sequence itself, as the bit of information coded by the accession numbers set forth in the present specification.

Nonetheless, Applicants appreciate the Examiner's concern with respect even to identity, and therefore have amended the present specification to specify that an accession number, as used in the present specification, is understood to represent the identity of the gene so-specified as of the priority filing date of the present application. Hence, the rejection under § 112 has been overcome and reconsideration is respectfully requested.

35 U.S.C. § 102

Claims 1-6, 8, 9, 11-17, 20-22, 29 and 38-42 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kostulas et al., *Stroke* 29:462-466 (1998). Specifically, the Examiner asserts that Kostulas teaches a method of instant independent claims 1 and 38 of injury assessment in an individual because Kostulas teaches "the pattern of expression of the number of cells which express II-8, MCP-1, MIP-1alpha, and MIP-1 beta as instant step (a), and comparison of the expression IL-8, as instant step (b). This rejection is traversed and reconsideration is respectfully requested.

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Present claim 1 is directed to a method of injury assessment in an individual. The method comprises the steps of: a. determining a pattern of expression exhibited by blood cells obtained from the individual, and b.

55 comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury, wherein the pattern of expression comprises patterns of gene expression, protein expression, or combinations thereof, and further wherein the injury database comprises organ specific injury database, disease specific injury database, or combinations thereof.

60 Present independent claim 38 is directed to a method of stroke injury assessment in an individual. The method comprises the steps of: a. obtaining a peripheral blood sample from the individual; b. capturing a pattern of expression; c. defining the pattern of expression; and d. comparing the pattern of expression to an injury database to assess stroke injury.

65 It is important to note that the term "pattern of expression," as employed by the Applicants, refers to a pattern derived from observation of expression across a database of genes, the database in the instant claims being comprised of multiple genes/molecules. The expression response profile of a single gene does not constitute the "expression pattern" according to the

70 present invention. For example, in the "Background of the Invention" section of the present specification, Applicants note that several investigators have determined specific gene responses induced by various injury states. Indeed, like Kostulas, Applicants note that Barone teaches the induction of interleukin-8 (IL-8), among other proteins, by brain stroke (page 3, third

75 paragraph).

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On page 15 of the instant specification, Applicants define "pattern of

expression" as referring to "the representation of molecules, including but not

limited to genes, proteins or combinations thereof, in an injury state, which are

upregulated, downregulated or embody no change." Significantly, Applicants

80   specify exemplary "expression methods" intended to "define" a pattern of

expression as "significance analysis" and "class prediction," both methods

which deal with population levels of statistics, not an individual level.

Further, Applicants note that the present specification at page 17 teaches that

"at least 10" molecules are "necessary to define a pattern of expression." A

85   pattern of expression is further depicted as being "captured" for a particular

injury state (page 22, line 5).

Applicants point, in particular, to the present disclosure on pages 22

and 23 for an illustration of how to experimentally determine a pattern of

expression. Note that such a determination requires, for example, ranking the

90   molecules of a captured pattern of expression by, for example, assigning some

ascending numerical value to the expression products, on the basis of their

expression strength. Once a pattern of expression is captured and defined, the

pattern of expression exhibited by an unknown blood cell sample may be

compared to the injury database (page 25, bottom, bridging to the top of page

95   26).

Applicants note that both independent claims require comparison to an

"injury database," which is defined on page 13 of the specification to refer to

"a database comprising a pattern of expression or patterns of expressions

indicative of a single or different states of injury. Applicants teach that such a

100   database is first established for a particular injury (page 22, line 6-9), by

capturing patterns of expression.

Hence, without the capture of a pattern of expression as required by

instant claims 1 and 38, and without generation of the injury database required

by instant claims 1 and 38, the present inventive methods cannot be practiced.

105   Kostulas, on the other hand, merely teaches the correlation of the

expression levels of the mRNA of a single protein, IL-8, "suggesting that IL-8

could be involved in recruiting blood PMNL to the sites of cerebral ischemia

(see Abstract, sentences beginning "Results" and "Conclusions"). Kostulas

fails to disclose any post-experimental processing of the levels derived, as

110   instantly required in order to capture and define the requisite "pattern of

expression" according to the present invention as set forth in present claims 1

and 38.

Further, Kostulas is investigating a potential role of IL-8 in "recruiting

blood PMNL to the sites of cerebral ischemia" (page 465, lines 6-7) for the

115   purpose of developing regiment to neutralize IL-8 in stroke victims (page 465,

column 2, lines 13-16). Kostulas does not teach or otherwise disclose the

generation of an injury database based on patterns of expression in order to

assess an injury.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a

120   single prior art reference of each element of the claims under consideration,

Alco Standard Corp. v. TVA, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986).

Kostulas fails to disclose methods of injury assessment comprising, inter alia,

determining a pattern of expression and comparing the pattern of expression

exhibited to an injury database to assess the injury as required by the present

125   invention defined by instant independent claim 1. Nor does Kostulas teach or

disclose methods of stroke injury assessment according to instant independent

claim 38, which requires the steps of, inter alia, capturing a pattern of

expression, defining the pattern of expression, and comparing the pattern of

expression to an injury database, as defined by the present specification.

130   Hence, the rejection of claims 1 and 38, and claims 2-6, 8, 9, 11, 17, 20-22,

29, and 39-42 dependent therefrom, under 35 U.S.C. §102 under Kostulas has

been overcome. Reconsideration is therefore respectfully requested.

          Claims 1-17, 20-22, and 29 are rejected under 35 U.S.C. § 102(e) as

being anticipated by U.S. Patent No. 6,316,197 to Das et al. ("Das").

135   Specifically, the Examiner asserts that Das teaches the methods of instant

independent claims 1 and 38 [it should be noted that instant claim 38 has not

been rejected on the basis of Das, so Applicants assume this mention is an

unintended artifact of it having been mentioned similarly in the prior rejection

basis], wherein the injury is exposure to a toxic agent. The Examiner further

140   asserts that Das teaches the pattern of gene expression of HCl and EIF-1,

where Das teaches that dozens of genes in peripheral blood are responsive to

SEP, which includes lipopolysaccharide, and to Anthrax, analysis of

peripheral blood samples, and "forms a pattern of expression," when

disclosing the observation that "the in vivo response reflected the pattern of

145   altered gene expression that we had seen in vitro." This rejection is traversed

and reconsideration is respectfully requested.

          Instant claim 1 is set forth in detail, supra. In particular, Applicants

reiterate that the inventive method defined by claim 1 is a method of injury

assessment, and requires, inter alia, establishment of an injury database,

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150 wherein the injury database comprises organ specific injury database, disease

specific injury database, or combinations thereof.

Das, on the other hand, discloses methods of diagnosing exposure to toxic

agents by taking samples of toxin-exposed and toxin-unexposed tissues from the same

individual, detecting an amount of protein/gene expression present in each,

155 determining the difference, and comparing this difference to a library of expected

expression for pre-determined toxic agents (see, e.g. Abstract).

Das, therefore, has a pre-determined database of toxins, based on

establishment of relative patterns of expression particular of a particular toxin.

Comparison of any generated pattern of expression, therefore, indicates,

160 theoreitically, exposure to a particular toxin according to its alignment with one of the

predetermined toxin databases. Applicants note also that Das teaches establishment

of the toxin database by relative comparison, not by absolute generation, of patterns

of expression. Importantly, Das is not assessing injury states by comparison to an

injury database, but is assessing toxin identity by comparison to databases of toxins.

165 The present inventive method of assessing injury states, on the other hand,

requires an injury data base, wherein the injury database comprises organ specific

injury database, disease specific injury database, or combinations thereof. The

comparison permits assessment of injury state, not exposure to and/or identity of a

chemical compound, as allegedly permitted by the databases of Das.

170 As previously noted above, anticipation under 35 U.S.C. § 102(b) requires the

disclosure in a single prior art reference of each element of the claims under

consideration, *Alco Standard Corp.* 1 U.S.P.Q.2d 1337, at 1341. Das fails to teach an

injury data base comprising either an organ specific database or a disease specific

database, as required by instant independent claim 1. The sole database disclosed by

175   Das is a toxin database. Hence, the rejection under 35 U.S.C. §102(e) under Das has

been overcome and reconsideration is respectfully requested.

35 U.S.C. § 103

Claims 1-17, 20-22, 29 and 38-42 are rejected under 35 U.S.C. § 103(a) as

being unpatentable over Kostulas in view of U.S. Patent No. 6,040,138 to Lockhart et

180   al. ("Lockhart"). Specifically, the Examiner asserts that Kostulas teaches the methods

of independent claims 1 and 38 of injury assessment in an individual, as set forth in

the § 102 rejection, supra. The Examiner notes, however, that Kostulas fails to teach

elements of claims 7 and 10, and does not teach application of the method to

microarrays, which the Examiner asserts to be a "clear intent" of the present

185   invention, "though the limitation never currently appears in the claims." With respect

to the secondary reference, the Examiner asserts that Lockhart teaches a method of

analyzing expression of nucleic acids whose expression is altered in a disease state,

comprising the steps of (a) determining a pattern of expression using a microarray

exhibited by blood cells, and comparing the pattern to a database to assess injury .

190   The Examiner further asserts that Lockhart expressly teaches the steps of I) isolating

RNA from the cells, ii) preparing a labeled probe using the isolated RNA, iii)

applying the probe to a microarray, and iv) measuring the level of the RNA, allegedly

according to instant claim 7, expressly teaches labeling the cDNA product, according

to instant claim 10, and further teaches the use of chemokines like interleukin 6, a

195   glycosylated protein disclosed in instant Table 1, and as recited in instant claims 12-

15. The Examiner concludes that it therefore would have been prima facie obvious to

one of ordinary skill in the art at the time the invention was made to use the

microarray and microarray methods of Lockhart to analyze the gene expression in

stroke as discussed by Kostulas, since Lockhart notes "It will be appreciated that the

200   methods of this invention can be used to monitor the expression of any desired gene

of known sequence or subsequence...[and that] genes of particular interest for

expression monitoring include genes involved in the pathways associated with various

pathological conditions and whose expression is thus indicative of the pathological

condition," such that the ordinary practitioner, motivated by Kostulas to detect gene

205   expression in stroke, would have been strongly motivated to use the microarray

method of Lockhart to determine which genes were involved in stroke in order to

permit diagnosis as taught by Lockhart.

The recitations of independent claims 1 and 38 have been set forth in detail

above. In addition, in the analysis of the 102 rejection under Kostulas, Applicants

210   delineated the insufficiencies of the Kostulas disclosure with respect to the present

independent claims. That is, Kostulas fails to disclose or suggest methods of injury

assessment comprising, inter alia, determining a pattern of expression and comparing

the pattern of expression exhibited to an injury database to assess the injury, as

required by the present invention defined by instant independent claim 1.

215   As noted in the prior traversal, Kostulas does not use the term "expression

pattern" in a manner that comports with the term "pattern of expression," as instantly

defined by the specification. Nor does Kostulas teach or disclose methods of stroke

injury assessment according to instant independent claim 38, which requires the steps

of, inter alia, capturing a pattern of expression, defining the pattern of expression, and

220   comparing the pattern of expression to an injury database, as defined by the present
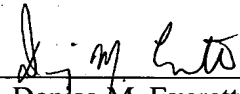
specification.

The secondary reference, Lockhart, is directed to methods of analyzing the

expression of one or more genes (see, e.g. claim 1, and Abstract). While Applicants

agree that Lockhart discloses subject matter that permits simultaneously monitoring

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225   the expression of a multiplicity of genes, and touts the method as effective for

monitoring gene expression "involving pathways associated with various pathological

conditions (column 4, lines 64-67), Applicants submit that Lockhart does not teach or

suggest the present methods of assessing an injury state, and does not overcome the

deficiencies of the primary reference with respect to teaching or disclosing, inter alia,

230   determining and defining a "pattern of expression" according to the present invention,

or an injury database derived from determining and defining such patterns of

expression for specific injury states, wherein the injury database comprises organ

specific injury database, disease specific injury database, or combinations thereof.

    To establish prima facie obviousness of the claimed invention, all the claim

235   limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981,

180 U.S.P.Q. 580 (CCPA 1974). The deficiencies of Kostulas are set forth in detail,

supra. Kostulas fails to teach or suggest, inter alia, "patterns of expression" defined

according to the present invention, or injury databases, wherein the injury database

comprises organ specific injury database or disease specific injury database, or

240   combinations thereof, and fails to disclose, specifically, an injury database for stroke

injury as required by instant claim 38. The secondary reference fails to address or

overcome these deficiencies. Hence, a prima facie case has not been established and

the rejection of claims 1 and 38, and the claims dependent therefrom has been

overcome. Reconsideration is therefore respectfully requested.

245   Applicants believe that the above represents a complete and effective response

to the rejections of the present claims under 35 U.S.C. §§ 112, 102, and 103. Hence,

reconsideration and an early allowance are respectfully requested.

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